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BUDAPEST

---------- Translated from Hungarian ----------

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---------- PRIORITY CERTIFICATE ----------

Serial No. P0200849 ----------

The National Office of Inventions certifies that --
Sanofi-Synthelabo, Paris (FR), ----------
filed a patent application in Hungary on March 6, 2002 ----------
under registration No. 9753/02, entitled ---------
New compounds. ----------

The enclosed copy is fully identic with the papers filed simultaneously with the application. -------

Budapest, February 14, 2003 ----------

This is a true extract: ----------

Illegible signature ----------

Szabó, Emilné ----------

Head of Patent Department ----------

The Hungarian Patent Office certifies in this priority certificate that the said applicant(s) filed a patent application at the specified date under the indicated title, application number and registration number. The attached photocopy is a true copy of specification filed with the application. -

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P02 00849 ---------- 06. 03. 2002 --

ers, in the liver, in the islands of the pancreas, in the renal cortex, in the lungs, and in certain tissues of the prostate and the small intestines. Significant DPP-IV activity can be observed furthermore in the body liquors (as for instance in the plasma, serum and urine). ----------

DPP-IV is a serine protease type enzyme, which has the unique specificity to cleave dipeptides from the N-terminals of peptides where the pre-terminal amino acid is primarily proline, or secondarily alanine. ----------

DPP-IV enzyme is responsible for the decomposition of the glucagon-like peptides, peptide-1 (GLP-1) and peptide-2 (GLP-2) in the body. The enzyme GLP-1 strongly stimulates the insulin production of the pancreas, thus it has a direct, favourable effect on the glucose homeostasis, therefore DPP-IV inhibitors are suitable for the treatment of non-insulin dependent diabetes mellitus (NIDDM). -----

Our aim was to prepare new, effective and safe DPP-IV inhibitors. ----------

We have found that the compounds of the general formula (I) wherein R^1 stands for: ----------

- one or two nitrogen-containing aromatic rings, preferably pyridyl, pyridazinyl, pyrimidinyl,

pyrazinyl, imidazolyl, pirazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, benzimidazolyl, indazolyl, benzothiazolyl, benzisothiazolyl, benzoxazolyl or benzisoxazolyl groups; which are, in a given case, mono- or disubstituted independently by one or two of the following groups: C1-4 alkyl group, C1-4 alkoxy group, a halogen atom, trihalogenomethyl group, methylthio group, nitro group, cyano group; ----------

- thienyl or furyl group, or ----------

- p-toluenesulfonyl group, or ----------

- the acyl group of formula R_{1a}-CO, wherein R_{1a} means a C1-4 alkyl group, phenyl group; phenyl, pyridyl or phenylethenyl group substituted with one or more alkyl- and/or alkoxy- or nitro-group or halogen atom; phenylethenyl group, or a phenylethyl group substituted with alkylene-dioxy group; piperidin-1-yl, 4-methyl-piperazin-1-yl, or pyrrolidin-1-yl group; ----------

B stands for ----------

- a group according to the formula (1) or (2) or (3); or----------

- a group of the formula (4), wherein m is 2 or 3;

or ----------

- a group of the formula (5) - wherein R^4 means a hydrogen atom or a C1-4 straight or branched alkyl group and n is 2 or 3; ----------

R^2 stands for a hydrogen atom or fluoro atom; ----

R^3 stands for a fluoro atom - ----------

as well as the salts, isomers and solvates of these compounds, having significant advantages as regards their activity, stability and toxicity. In agreement with the accepted terminology, the configuration of carbon-2 of the fluoropyrrolidine group is favourably S, whereas that of carbon-4 is S or R. ----------

Especially advantageous are the compounds wherein the meaning of R^1 is pyrazin-2-yl or 5-cyanopyridin-2-yl group, both R^2 and R^3 stand for fluoro atoms, and B means a piperidin-4-yl group; such compounds are for instance 1-{[1-(pyrazin-2-yl)-piperidin-4-yl]amino}acetyl-2-(S)-cyano-4,4'-difluoropyrrolidine and 1-{[1-(5-cyanopyridin-2-yl)piperidin-4-yl]amino}acetyl-2-(S)-cyano-4,4'-difluoropyrrolidine. ----------

The compounds of the general formula (I) according to our invention can be prepared by the alkylation of the primary amines of the general formula (II)

- wherein the meanings of R^1 and B are the same as given above - with chloroacetyl derivatives of the general formula (III) - wherein the meanings of R^2 and R^3 are as given above - and, if desired, by transforming the resulting compounds into one of their salts or solvates (Figure 1.). ----------

In the course of the alkylation the chloroacetyl derivatives of the general formula (III) are applied in excess, and the resulting hydrochloric acid is bound by various acid binding agents, preferably by a strong base, such as for instance 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 2-*terc*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (PBEMP) known as super base - bound to a resin. The reaction is preferably performed at a temperature between 25 and 55 °C. ----------

The primary amines of the general formula (II) are prepared in a two-step reaction (Figure 2.). In the first step the starting cyclic secondary amines of the general formula (IV) - wherein the meaning of Y is a hydrogen atom, acetyl or *tert*-butoxycarbonyl group, - are arylated, preferably with the aryl halogenides of the general formula (X), wherein the meaning of R^1 is the same as given

above and X stands for a halogen atom. Depending on the meaning of R^1 the arylation can be carried out in polar, protic or aprotic solvents, between 25 and 150 °C, preferably in alcohols (ethanol, *n*-butanol, *n*-pentanol), or without solvent in a microwave oven, using an acid binder, for instance the excess of the amine or DBU. ----------

For starting material the free amines or protected secondary amines of the general formula (IV) - known from the literature - are used, thus 4-acetaminopiperidine (B = formula (1), Y = $COCH_3$) (Chem. Abstr. **1996**, *64*, 6664); 4-*tert*-butoxycarbonylaminopiperidine (B = formula (1), Y = $COOC(CH_3)_3$) (J. Med. Chem. **1999**, *42*, 2706); 3-(S)-*tert*-butoxycarbonylaminopiperidine (B = formula (2)) and 3-(S)-*tert*-butoxycarbonylaminopyrrolidine (B = formula (3)) (Synth. Comm. **1998**, *28*, 3919); in the last two cases (Y = $COOC(CH_3)_3$); ----------

3-*exo*-[(*tert*-butoxycarbonyl)amino]-8-azabicyclo-[3.2.1]octane, 3-*endo*-[(*tert*-butoxycarbonyl)-amino]-8-azabicyclo[3.2.1]octane (B = formula (4), m = 2) (J. Med. Chem. **1991**, *34*, 656); 3-*exo*-[(*tert*-butoxycarbonyl)amino]-9-azabicyclo[3.3.1]-nonane and 3-*endo*-[(*tert*-butoxycarbonyl)amino]-9-azabicyclo[3.3.1]nonane (B = formula (4), m = 3)

(J. Med. Chem. **1993**, *36*, 3720) (Y = $COOC(CH_3)_3$); - diaminoethane (B = formula (5), wherein R^4 = H, n = 2, Y = H); diaminopropane (B = formula (5), wherein R^4 = H, n = 3, Y = H); *N*-methyl-*N'*-(*tert*-butoxycarbonyl)diaminoethane (B = formula (5), wherein R^4 = Me, n = 2, Y = $COOC(CH_3)_3$) (J. Med. Chem. **1990**, *33*, 97); *N*-methyl-*N'*-(*tert*-butoxycarbonyl)diaminopropane (B = formula (5), wherein R^4 = Me, n = 3, Y = $COOC(CH_3)_3$) (Org. Lett. **2000**, *2*, 2117). ----------

In the second step the protecting group Y is removed from the arylated amine of the general formula (V) - wherein the meanings of R^1 and B are the same as defined above - by acidic hydrolysis. The reaction is carried out in aqueous hydrochloric acid or in hydrogen chloride solution in ethanol at a temperature between 25 and 78 °C to yield the aliphatic or cyclic primary amines of the general formula (II) - wherein the meanings of R^1 and B are the same as defined above. ----------

If R^1 stands for an acyl group of the formula R_{1a}-CO, the compounds of the general formula (IV) - wherein the meaning of Y is *tert*-butoxycarbonyl group - are reacted with the acid derivatives of the general formula R^{1a}-COZ - wherein the meaning

of Z is a leaving group (preferably a chloro atom) - preferably at a temperature around 0 °C, using an inorganic or organic base, preferably triethylamine as acid binding agent. ----------

From the compounds of the general formula (V) the protecting group Y is cleaved under acidic conditions, preferably by using trifluoroacetic acid in dichloromethane solution, at 0 - 30 °C, to obtain the the amines of the general formula (II), wherein the meaning of R^1 is the group of formula R_{1a}-CO. ----------

The chloroacetylcyano compounds of the general formula (III) - wherein the meanings of R^2 and R^3 are the same as defined above - are prepared in a four-step synthesis (Figure 3.). ----------

The starting compounds are the fluoroproline derivatives of the general formula (VI), preferably L-fluoroproline derivatives - wherein the meanings of R^2 and R^3 are the same as defined above - with a nitrogen protected with a *tert*-butoxycarbonyl group. These compounds can be prepared by methods described in the literature (Tetrahedron Lett. **1998**, *39*, 1169). In the first step a mixed anhydride is prepared with pivaloyl chloride, then the carbamoyl derivatives of the general formula (VII)

- wherein the meanings of R^2 and R^3 are the same as defined above - are formed with aqueous ammonia. - The reaction is preferably carried out in a halogenated solvent ($CHCl_3$, CH_2Cl_2), at 0 - 25 °C. ---- In the second step the *tert*-butoxycarbonyl group is removed in hydrogen chloride solution in ethanol. The hydrolysis takes place at 0 - 25 °C and the hydrochlorides of the carboxamides of the general formula (VIII) - wherein the meanings of R^2 and R^3 are the same as defined above - are obtained. ----------

The fluoropyrrolidinecarboxamides of the general formula (VIII) thus obtained are in the third step acylated with chloroacetyl chloride, preferably at 0 °C, in a halogenated solvent ($CHCl_3$, CH_2Cl_2). Thus chloroacetylcarbamoyl derivatives of the general formula (IX) - wherein the meanings of R^2 and R^3 are the same as defined above - are formed. --- In the fourth step the chloroacetylcarbamoyl derivatives of the general formula (IX) are dehydrated to yield the chloroacetylcyano derivatives of the general formula (III) - wherein the meanings of R^2 and R^3 are the same as defined above. Dehydration is preferably carried out with oxalyl chloride, in the presence of DMF, in acetonitrile

at a temperature below 0 °C.

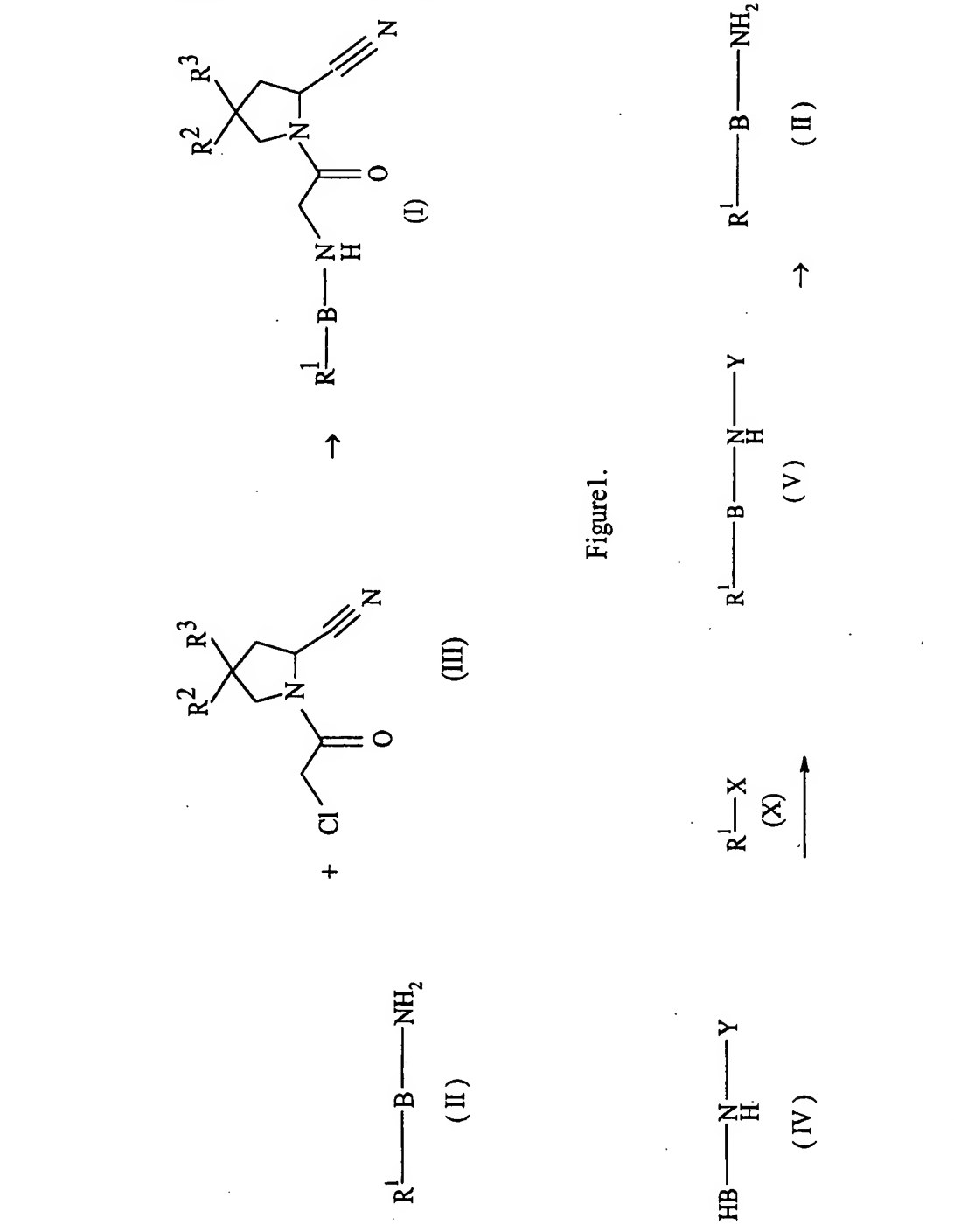
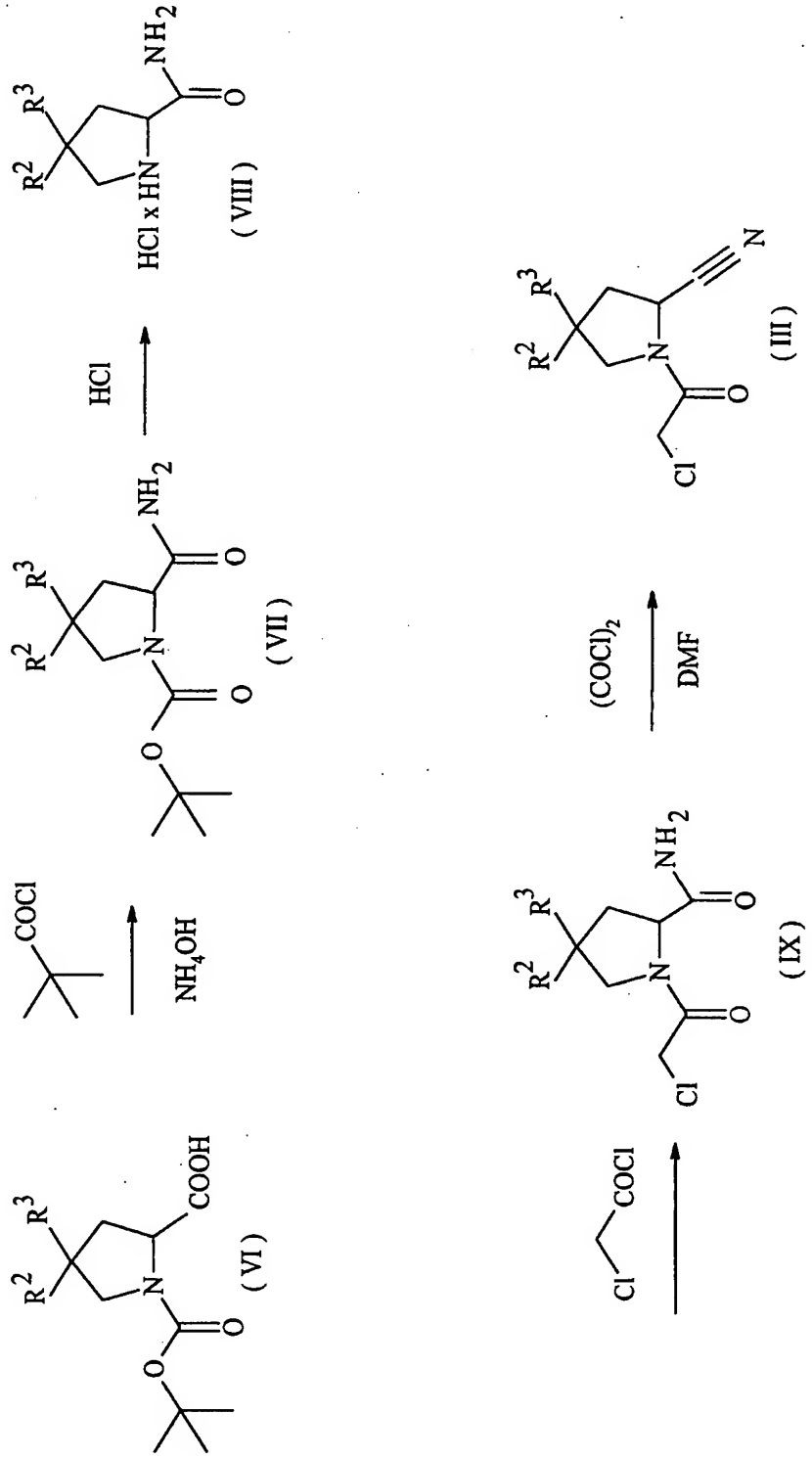


Figure1.

---------- Figure 2 ----------


HCl x HN
NH2
O
R2
R3
(VIII)
HCl
N
Cl
(III)
(COCl)2
DMF
(VII)
COCl
NH4OH
(IX)
Cl
COCl
(VI)
COOH

---------- Figure 3 ----------

Biological investigations ----------

DPP-IV enzyme inhibitory activities of the compounds with the general formula (I) were determined by the following method: ----------

Applied conditions of the assay: ----------

DPP-IV. source: ----------

------- solubilized crude extractum from CaCo/Tc-7

------- cells ----------

------- content: 0.8-1 µg/assay ----------

Substrate: H-Gly-Pro-AMC (Bachem) ----------

Reaction: ----------

------- 1 hour preincubation with samples at

------- 37 °C, ----------

------- 30 min reaction time at 37 C° ----------

Stop solution: 1M Na-acetate buffer (pH = 4.2) ---

Reaction mixture: ----------

------- 10 µl enzyme solution ----------

------- 10 µl test compound or assay buffer ------

------- 55 µl assay buffer ----------

------- 25 µl substrate ----------

------- 300 µl stop solution ----------

Measurement: ----------

------- spectrofluorometric determination by Tecan

------- plate reader ----------

------- (Ex: 360 nm Em: 465 nm) ----------

The reaction of the DPP-IV enzyme and the H-Gly-Pro-AMC substrate is recorded by the liberation of AMC (7-amino-4-methylcoumarin) at 37 °C in 100 mM Tris-HCl, pH = 7.5 (assay buffer). Standard curve of AMC is linear up to 31.25 µM concentration, that is why we used the relative fluorescence unit (RFU) of the AMC formed. It is detected by using 360 nm excitation and 465 emission filters (30 µs integration time, Gain 25, No. of Flashes 50) by Tecan Spectrofluor Plus plate reader. Under these conditions enzyme reaction is linear for at least 30 min, and the enzyme dependence is linear up to 2.5 µg protein (up to 700 RFU). Using 1-0.8 µg of extracted protein K_m for H-Gly-Pro-AMC is 50 µM. Substrate concentrations higher than 500 µM caused fluorescency detection problems (inner filter effect) that can be solved by dilution of the samples. ----------

The assay is designed to detect the active inhibitors as efficiently as possible, using a 60 min preincubation time at 37 °C. The assay is conducted by adding 0.8-1 µg protein extract in 10 µl enzyme solution (using assay buffer: 100 mM Tris-HCl, pH = 7.5) to the wells containing the test compounds in 10 µl volume and the 55 µl assay

buffer (65 µl assay buffer in the case of controls). After the preincubation period, the reaction is started by the addition of 25 µl 1 mM H-Gly-Pro-AMC substrate solution (250 µM final concentration). The final test volume is 100 µl and the test solution contains 1 % DMSO coming from the test compounds solution. Reaction time is 30 min at 37 °C, and the reaction is stopped by adding 300 µl 1M Na-acetate buffer, pH = 4.2. The fluorescence (RFU) of AMC formed is detected using 360 nm excitation and 465 emission filters in Tecan spectrofluor Plus plate reader (30 µs integration time, Gain 25 No. of Flashes 50). --------

Inhibition % are calculated using the RFU of control and RFU of blank. ----------

IC_{50} values characteristic for the enzyme inhibitory effect of the compounds of the general formula (I) according to the invention are smaller than 100 nM. The compounds of the general formula (I) and their salts, solvates and isomers can be formulated to orally or parenterally applicable pharmaceutical preparations by known methods, by mixing them with one or more pharmaceutically accepted excipients. ----------

Daily dose of the compounds of the general formula

(I) may depend on several factors, like the nature and seriousness of the disease of the patient, the mode of application and the compound itself. -----

Further details of the invention are demonstrated by the examples below, without limiting the claims to the examples. ----------

Example 1: ----------

1-{[1-(Pyrazin-2-yl)piperidin-4-yl]amino}acetyl-2-(S)-cyano-4,4'-difluoro-pyrrolidine ----------

In the general formula (I) R^1 stands for a pyrazin-2-yl group, B for a piperidin-4-yl group (group of formula (1)), R^2 and R^3 mean for fluoro atoms. ---

a.) 1-(Pyrazin-2-yl)-4-acetaminopiperidine general formula (V) - wherein Y = $COCH_3$, B = group of formula (1) ----------

To the solution made of 0.45 ml (5 mmol) of chloropyrazine and 15 ml of *n*-pentanol 1.6 g (10 mmol) of 4-acetamidopiperidine monohydrate is added. The mixture is refluxed for 14 hours, then evaporated. The residue is purified by column chromatography using an ethyl acetate - methanol - 25 % aqueous ammonia solution 17:3:1 mixture as eluent. 0.81 g (76 %) of the title compound is obtained. ----------

M.p.: 158 - 160 °C. ^{1}H-NMR (DMSO-d_6): δ 1.34 (dq,

2H), 1.78 (m, 2H), 3.03 (dt, 2H), 3.74-3.89 (m, 1H), 4.21 (td, 2H), 7.77 (d, 1H, 3'-H), 7.80 (s, 1H, NH), 8.05 (dd, 1H, 5'-H), 8.31 (d, 1H, 6'-H). -

b.) 1-(Pyrazin-2-yl)-4-aminopiperidine general formula (II) - wherein R^1 and B are the same as above ----------

697 mg (3.2 mmol) of 1-(pyrazin-2-yl)-4-acetaminopiperidine is dissolved in 15 ml of 2*N* hydrochloric acid and boiled for 8 hours. The mixture is cooled, made alkaline with 20 % NaOH solution and extracted with 4 × 20 ml of dichloromethane. The combined organic layer is dried over sodium sulphate and evaporated. The title product is obtained in the form of yellow crystals: 292 mg (52 %). ----------

Mp.: 113 - 115 °C. ^{1}H-NMR (DMSO-d_6-$CDCl_3$): δ 1.09-1.36 (m, 2H), 1.78 (d, 2H), 2.78-3.31 (m, 4H), 3.54 (m, 1H), 7.76 (d, 1H, 3'-H), 8.03 (dd, 1H, 5'-H), 8.29 (d, 1H, 6'-H). ----------

The same product can be obtained by boiling 0.71 ml (8 mmol) of chloropyrazine, 1.4 g (7 mmol) of 4-*tert*-butoxycarbonylaminopiperidine and 1.27 ml (8.5 mmol) of DBU in 40 ml of *n*-pentanol for 18 hours, evaporating the solution and purifying the product by column chromatography, using EtOAc - *n*-

hexane - chloroform 3:1:1 mixture as eluent. The resulting 1.10 g of 1-(pyrazin-2-yl)-4-*tert*-butoxycarbonylaminopiperidine of the general formula (V), wherein Y = $COOC(CH_3)_3$, m.p.: 132 - 133 °C, is stirred in 20 ml of hydrogen chloride solution in ethanol for 4 hours at room temperature. 0.5 g (70 %) of 1-(pyrazin-2-yl)-4-aminopiperidine hydrochloride crystallises from the solution. On the effect of alkali the hydrochloride salt transforms into the above compound, 390 mg (80 %). ----------

c.) 1-(*tert*-Butoxycarbonyl)-2-(S)-carbamoyl-4,4'-difluoropyrrolidine compound of the general formula (VII) - wherein R^2 and R^3 are fluoro atoms -- 5.7 g (22.7 mmol) of 1-(*tert*-butoxycarbonyl)-4,4'-difluoro-2-(S)-proline is dissolved in 57 ml of dichloromethane and to the solution 3.8 ml (27.2 mmol) of triethylamine is added. To the resulting mixture, at -15 °C 3 ml (25 mmol) of pivaloyl chloride is added drop by drop and the mixture is stirred at this temperature for 1 hour, then 7 ml of 25 % aqueous ammonia solution is added drop by drop and the mixture is stirred for 1 hour. The reaction mixture is washed with water, with 1 *N* NaOH solution, then with water, dried over sodium sulphate and evaporated. On addition of diethyl

ether 3.94 g (69 %) of the above product crystallises. ----------

M.p.: 136-138 °C. ^{1}H-NMR ($CDCl_3$): δ 1.48 (s, 9H); 2.3-2.9 (m, 3-CH_2), 3.69 (br, minor) + 3.86 (m, major)(5-CH_2), 4.53 (br, 2-CH). 6.0 (br, major) + 6.81 (br, minor)(NH_2). ----------

d.) 4,4'-Difluoropyrrolidine-2-(S)-carboxamide hydrochloride compound of the general formula (VIII) - wherein R^2 and R^3 are fluoro atoms ----------

3.93 g (15.7 mmol) of 1-*tert*-butoxycarbonyl-2-(S)-carbamoyl-4.4'-difluoropyrrolidine is dissolved in 75 ml of 25 % hydrogen chloride solution in ethanol and stirred at room temperature for 4 hours. To the resulting suspension 150 ml of diethyl ether is added, the resulting white crystalline material is filtered off. 2.55 g (87 %) of the above product is obtained. ----------

M.p.: 232-233 °C. ^{1}H-NMR (DMSO-d_6): δ 2.43-2.51 (m, minor) + 2.81-3.05 (m, major)(3-CH_2), 3.71 (t, 2H, 5-CH_2), 4.46 (t, 1H, 2-CH), 7.81 (s, 1H,) + 8.12 (s, 1H)(NH_2), 10.12 (br, 2H, NH_2^+). ----------

e.) 1-Chloroacetyl-2-(S)-carbamoyl-4,4'-difluoropyrrolidine compound of the general formula (IX) - wherein R^2 and R^5 are fluoro atoms ----------

2.54 g (13.6 mmol) of 4,4'-difluoro-pyrrolidin-2-

(S)-carboxamide hydrochloride is suspended in 25 ml of dichloromethane and to the suspension 4.1 ml (29.3 mmol) of triethylamine and 4 mg (0.03 mmol) of 4-dimethylaminopyridine is added. To the resulting mixture a solution, 1.2 ml (15 mmol) of chloroacetyl chloride in 20 ml of dichloromethane is added below -10 °C drop by drop. After 1 hour of stirring the suspension is poured onto 450 ml of ethyl acetate, the precipitated triethylamine hydrochloride is filtered off, the filtrate is evaporated and purified by chromatography using chloroform - methanol 4:1 mixture as eluent. 3.0 g (97 %) of the above product is obtained in the form of colourless oil. ^{1}H-NMR (DMSO-d_6): δ 2.34-2.52 (m, 1H) + 2.66-2.83 (m, 1H)(3-CH_2), 4.07-4.29 (m, 2H, 5-CH_2), 4.40 (qv, 2H, CH_2Cl), 4.71 (m, 1H, 2-CH), 7.17 (br, 1H,) + 7.42 (d, 1H)(NH_2). ------

f.) <u>1-Chloroacetyl-2-(S)-cyano-4,4'-difluoropyrrolidine compound of the general formula (III) - wherein R^2 and R^3 are fluoro atoms</u> ----------

340 mg (1.5 mmol) of 1-chloroacetyl-2-(S)-carbamoyl-4,4'-difluoro-pyrrolidine is dissolved in 10 ml of acetonitrile and to the solution 0.15 ml of dimethylformamide is added. The mixture is cooled to -25 °C and a solution of 0.15 ml (1.73

mmol) of oxalyl chloride in 2 ml of acetonitrile is added drop by drop. The mixture is stirred at room temperature for 2 hours then evaporated. The residue is dissolved in dichloromethane and washed with saturated sodium hydrogen carbonate solution. The organic layer is dried over sodium sulphate and evaporated. The residue is purified by chromatography using chloroform - methanol 9:1 mixture as eluent. 209 mg (67 %) of the desired product is obtained as a yellow oil. ^{1}H-NMR ($CDCl_3$): δ 2.76-2.98 (m, 2H, 3-CH_2), 3.92-4.26 (m, 2H, 5-CH_2), 4.46 (qv, 2H, CH_2Cl), 5.11 (m, 1H, 2-CH). ----------

g.) 1-{[1-(Pyrazin-2-yl)piperidin-4-yl]amino}acetyl-2-(S)-cyano-4,4'-difluoropyrrolidine dihydrochloride ----------

63 mg (0.32 mmol) 1-(pyrazin-2-yl)-4-aminopiperidine and 65 mg (0.32 mmol) of 1-chloroacetyl-2-(S)-cyano-4,4'-difluoropyrrolidine are dissolved in 20 ml of acetonitrile and to the solution 285 mg (0.73 mmol) of PBEMP is added. The mixture is stirred at 55 °C for 8 hours, then the resin is filtered off and the filtrate is evaporated. The residue is purified by chromatography using chloroform - methanol 9:1 mixture as eluent. 72 mg (60 %) of the above product is obtained in

the form of colourless oil, which on treatment with hydrogen chloride solution in ether gives the dihydrochloride salt. ----------

Mp: 146-147 °C. ^{1}H-NMR (DMSO-d_6): δ 1.54 (m, 2H), 2.15 (m, 2H), 2.80-2.95 (m, 4H), 4.20-4.25 (m, 4H), 4.55 (d, 2H,), 5.20 (t, 1H), 7.00 (d, 1H), 7.87 (dd, 1H), 8.50 (d, 1H); 9.38 (br, 2H). ------

Example 2: ----------

1-{[1-(5-Cyanopyridin-2-yl)piperidin-4-yl]-------- amino}acetyl-2-(S)-cyano-4,4'-difluoropyrrolidine dihydrochloride ----------

In the general formula (I) R^1 is a 5-cyanopyridin-2-yl group, B stands for the group of formula (1), R^2 and R^3 are fluoroatoms. ----------

The compound is prepared according to Example 1. using 5-cyano-2-chloropyridine instead of chloropyrazine. The desired title compound is obtained in the form of white crystals in a yield similar to that of Example 1. ----------

M.p.: 146-147 °C. ^{1}H-NMR (DMSO-d_6): δ 1.56 (m, 2H), 2.15 (d, 2H), 2.92 (m, 4H), 4.20 (m, 4H), 4.55 (d, 2H), 5.20 (t, 2H), 7.01 (d, 1H), 7.88 (d, 1H), 8.49 (dd, 1H), 9.38 (d, 1H). ----------

Example 3: ----------

1-{[8-(Pyrazin-2-yl)-8-azabicyclo[3.2.1]octan-3-

yl]-*exo*-amino}acetyl-2-(S)-cyano-4,4'-difluoropyrrolidine ----------

In the general formula (I) R^1 is a pyrazin-2-yl group, B stands for the group of formula (5) - where m is 2, R^2 and R^3 are fluoroatoms. ----------

a.) 3-*exo*-[(*terc*-Butoxycarbonyl)amino]-8-(pyrazin-2-yl)-8-azabicyclo[3.2.1]octane compound of the general formula (V) - wherein the meaning of B is the group of formula (5) - where m is 2, Y stands for a $-COOC(CH_3)_3$ group. ----------

The solution of 0.54 ml (6 mmol) of chloropyrazine, 1.13 g (6 mmol) of 3-*exo*-[(*tert*-butoxycarbonyl)amino]-8-azabicyclo[3.2.1]octane and 0.97 ml (6.5 mmol) of diazabicyclo[5.4.0]undecene in 40 ml of *n*-pentanol is boiled for 50 hours. The resulting mixture is evaporated in vacuum, the residue is dissolved in dichloromethane, washed with water, dried over sodium sulphate. After purification by chromatography (ethyl acetate - *n*-hexane - chloroform 3:1:1) 0.55 g (36 %) of title compound is obtained. ----------

Mp.: 122-123 °C. ^{1}H-NMR (DMSO-d_6): δ 1.34 (s, 9H); 1.44-1.66 (m; 2H), 1.67-1.99 (m, 6H), 3.88 (m, 1H), 4.56 (bs, 2H), 6.59 (d, 1H), 7.77 (d, 1H), 8.07 (dd, 1H), 8.17 (d, 1H). ----------

b.) 3-*exo*-Amino-8-(pyrazin-2-yl)-8-azabicyclo-----[3.2.1]octane compound of the general formula (II) - wherein the meanings of R^1 and B are the same as in the previous a.) step ----------

385 mg (1.26 mmol) of 3-*exo*-[(*tert*-butoxycarbonyl)amino]-8-(pyrazin-2-yl)-8-azabicyclo[3.2.1]-octane is stirred for 3 hours at room temperature with 20 ml of 12 % hydrogen chloride solution in ethanol. To the resulting white suspension 20 ml of water is added, the pH is adjusted to >10 with 40 % potassium hydroxide solution and the mixture is extracted with dichloromethane. The organic layer is dried over sodium sulphate and evaporated. The residue is purified by chromatography (ethyl acetate - methanol - 25 % aqueous ammonia 7:3:1) to obtain 167 mg (65 %) of title compound in the form of an oily material. ^{1}H-NMR (DMSO-d_6): δ 1.29 (t, 2H), 1.62-1.83 (m, 4H), 1.84-2.00 (m, 2H), 3.12 (sp, 1H), 4.57 (dd, 2H), 7.74 (d, 1H), 8.05 (dd, 1H), 8.15 (d, 1H). ----------

c.) 1-{[8-(Pyrazin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl]-*exo*-amino}acetyl-2-(S)-cyano-4,4'-difluoro-pyrrolidine dihydrochloride ----------

167 mg (0.82 mmol) of 3-*exo*-amino-8-(pyrazin-2-yl)-8-azabicyclo[3.2.1]octane and 170 mg (0.815

mmol) of 1-chloroacetyl-2-(S)-cyano-4,4'-difluoro-pyrrolidine are dissolved in 20 ml of acetonitrile and 600 mg (1.6 mmol) of PBEMP is added to the solution. The mixture is stirred at 55 °C for 16 hours and the resin is filtered off. The residue is purified by chromatography (chloroform - methanol 9:1). After acidification with hydrogen chloride solution in ethanol and precipitation with diethyl ether 88 mg (24 %) of title compound is obtained in the form of yellow crystals. ---------

Mp: 238-240 °C. ^{1}H-NMR (DMSO-d6): δ 1.70-1.82 (m, 4H), 1.95-2.15 (m, 4H), 2.79-3.01 (m, 2H), 3.94-4.27 (m, 5H), 4.68 (s, 2H), 5.15 (m, 1H), 7.87 (d, 1H), 8.15 (dd, 1H), 8.29 (d, 1H), 9.01 (bs, 2H). ----------

---------- 2002/4 ----------

---------- Claims ----------

1. The compounds of the general formula (I) - wherein R^1 means ----------

- one or two nitrogen-containing aromatic rings, preferably a pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, imidazolyl, pirazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, benzimidazolyl, indazolyl, benzothiazolyl, benzisothiazolyl, ben-

zoxazolyl or benzisoxazolyl groups; which are, in a given case, independently mono- or disubstituted by one or two of the following groups: C1-4 alkyl group, C1-4 alkoxy group, a halogen atom, trihalogenomethyl group, methylthio group, nitro group, cyano group; or ----------

- thienyl or furyl group; or ----------

- p-toluenesulfonyl group; or ----------

- acyl group of formula R_{1a}-CO, wherein R_{1a} means a C1-4 alkyl group, phenyl group; phenyl, pyridyl or phenylethenyl group substituted with one or more alkyl- and/or alkoxy- or nitro-group or halogen atom; phenylethenyl or phenylethyl group substituted with alkylene-dioxy group; piperidin-1-yl, 4-methylpiperazin-1-yl, pyrrolidin-1-yl group, ---

B stands for ----------

- a group of formula (1) or (2) or (3); or -------

- a group of formula (4), wherein m is 2 or 3; or-

- a group of formula (5) - wherein R^4 means a hydrogen atom or a C1-4 straight or branched alkyl group and n is 2 or 3; ----------

R^2 stands for a hydrogen atom or fluoro atom; ----

R^3 stands for a fluoro atom - ----------

as well as the salts, isomers and solvates of these compounds. ----------

2. The compounds of the general formula (I) according to claim 1. - wherein R^1 means a pyrazin-2-yl group or a pyridyl group substituted with a cyano group; B means a piperidin-4-yl group, R^2 and R^3 are fluoro atoms, as well as the salts, isomers and solvates of these compounds. ----------

3. 1-{[1-(Pyrazin-2-yl)piperidin-4-yl]amino}acetyl-2-(S)-cyano-4,4'-difluoropyrrolidine. --------

4. 1-{[1-(5-Cyanopyridin-2-yl)piperidin-4-yl]-amino}acetyl-2-(S)-cyano-4,4'-difluoropyrrolidine.

5. 1-{8-[Pyrazin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl]-exo-amino}acetyl-2-(S)-cyano-4,4'-difluoropyrrolidine. ----------

6. Pharmaceutical preparations, characterised by containing a compound of the general formula (I) - wherein the meanings of R^1, B, R^2 and R^3 are the same as defined in Claim 1 - or an isomer or solvate thereof in the form of the free compound or of a salt, and at least one pharmaceutically acceptable excipient or diluent. ----------

7. A process for the preparation of the compounds of the general formula (I) - wherein the meanings of R^1, B, R^2 and R^3 are the same as defined in Claim 1 - characterised by reacting a compound of the general formula (II) - wherein the meanings of

R^1 and B are as defined above - with a compound of the general formula (III) - wherein the meanings of R^2 and R^3 are as defined above - and separating the resulting compound of the general formula (I) or its salt from the reaction mixture. ----------

8. Use of a compound of the general formula (I) - wherein the meanings of R^1, B, R^2 and R^3 are the same as declared in Claim 1 - to prepare pharmaceutical preparations suitable to inhibit the activity of the DPP-IV enzyme, and thus suitable for the treatment of diseases related with the DPP-IV enzyme concentration. ----------

9. A process for the inhibition of the DPP-IV enzyme and for the treatment of diseases related with DPP-IV enzyme concentration, characterised by using a compound of the general formula (I) as defined in Claim 1 in therapeutically effective amount, in the form of the free compound, or of a salt. ----------

10. Compounds of the general formula (II) - wherein the meanings of R^1 and B are as defined in claim 1 - as well as their isomers and salts. ----

11. Compounds of the general formula (II) - wherein the meanings of R^2 and R^3 are as defined in claim 1 - as well as their isomers. ----------

12. Compounds of the general formula (V) - wherein the meanings of R^1 and B are as defined in claim 1, Y stands for an acetyl or *tert*-butoxycarbonyl group- as well as their isomers and salts. -------

13. Compounds of the general formula (VII) - wherein the meanings of R^2 and R^3 are as defined in claim 1 - as well as their isomers. ----------

14. Compounds of the general formula (VIII) - wherein the meanings of R^2 and R^3 are as defined in claim 1 - as well as their isomers and salts -----

15. Compounds of the general formula (IX) - wherein the meanings of R^2 and R^3 are as defined in claim 1. - as well as their isomers. ----------

The Representative in the name of the Applicant: --
L.S.: Sanofi-Synthelabo ----------
----- CHINOIN Rt. ----------
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P02 00849 ----------
Novel compounds ---------- 2002/4 --
Applicant: Sanofi-Synthelabo, Paris, France ------
---------- 3/1 --
L.S.: Sanofi-Synthelabo ----------
----- CHINOIN Rt. ----------
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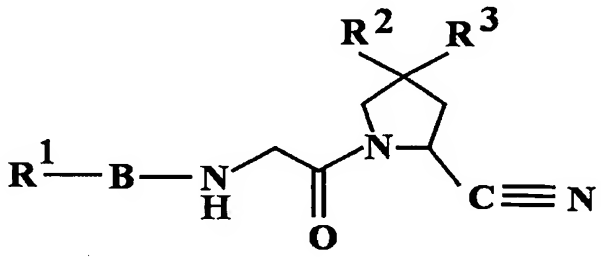

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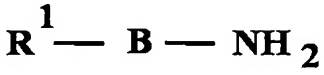

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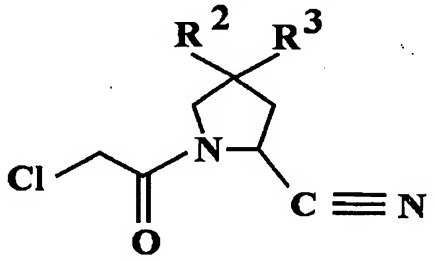

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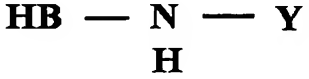

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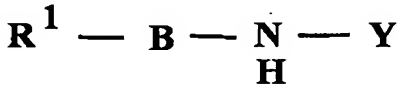

(V)

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Novel compounds ---------- 2002/4 --

Applicant: Sanofi-Synthelabo, Paris, France ------

---------- 3/2 --

L.S.: Sanofi-Synthelabo ----------

----- CHINOIN Rt. ----------

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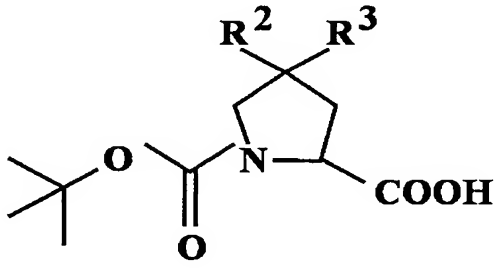

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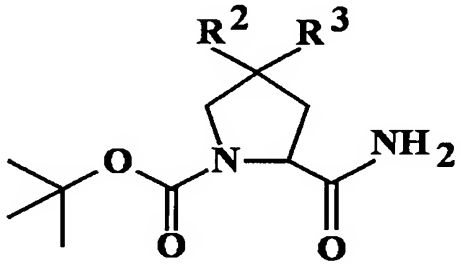

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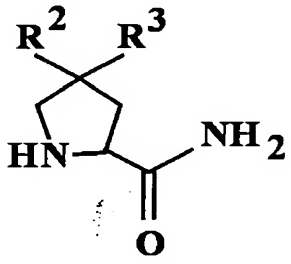

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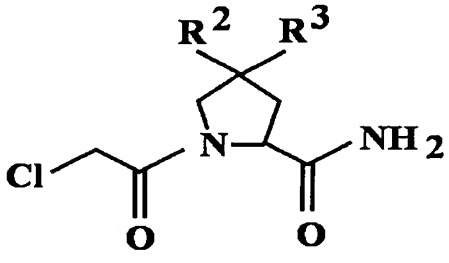

(IX)

$R^1 — X$ (X)

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Novel compounds ---------- 2002/4 --

Applicant: Sanofi-Synthelabo, Paris, France ------

---------- 3/3 --

L.S.: Sanofi-Synthelabo ----------

----- CHINOIN Rt. ----------

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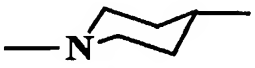

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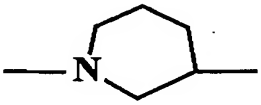

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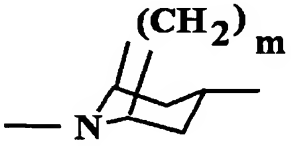

(4)

$$-N(R^4)-(CH_2)_n- \qquad (5)$$

04/KO-64707 OFFI - Hitelesen bizonyítom, hogy ez a fordítás az eredeti anyaggal mindenben megegyezik. Budapest, 2004. szeptember 15. ----------
Az Országos Fordító és Fordításhitelesítő Iroda Rt. vezérigazgatója helyett ----------

No. 04/KO-64707 ----------
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Budapest, 15th September, 2004 ----------
for the Director General ----------

No. 64707 /1999...
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Budapest, 16. 09. /1999.

Director

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